



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

AUG 16 2002

Date:

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Rec'd 8/23/02
16

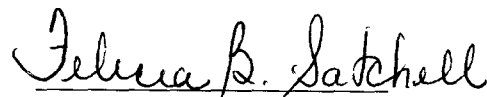
New Dietary Ingredient: *trans*-Resveratrol

Firm: InterHealth Nutraceuticals, Inc.

Date Received by FDA: September 28, 2001

90-Day Date: December 27, 2001

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.


Felicia B. Satchell

95S-0316

RPT101



DEC 12 2001

Mr. Shil C. Kothari
Product Development Manager
InterHealth Neutraceuticals, Inc.
5451 Industrial Way
Benicia, California 94510

Dear Mr. Kothari:

This is in response to your recent correspondence to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. 350b(a)(2). Your undated notification, that was received and filed by FDA on September 28, 2001, informed us of your intent to market a dietary supplement containing the new dietary ingredient "*trans*-Resveratrol." You describe the source of this new dietary ingredient as the root extract of *Polygonum cupdatum* (Siebold & Zucc.) with the trade name Protokin® (RSV-5000 powder) that provides a standardized level (50%) of *trans*-Resveratrol.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce. This information must include the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your notification and other published reports in the scientific literature and has made the following determinations. First, *trans*-Resveratrol is excluded from the definition of a "dietary supplement" under 21 U.S.C. 321(ff)(3)(B), because it is an article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and made public

in the U. S.¹ The purpose of this research underway is to investigate the use of *trans*-Resveratrol in combination with nucleoside analogs in the treatment of human immunodeficiency virus infection.

FDA authorized *trans*-Resveratrol (which is also known as "resveratrol" or 3,5,4'-trihydroxystilbene) to be an investigational new drug on January 30, 2001. The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined a "new dietary ingredient" as one that was marketed in the U.S. on or after October 15, 1994. This office does not have any information that indicates that *trans*-Resveratrol was legally marketed as a dietary ingredient in the U.S. before October 15, 1994.

Second, the agency has concerns about the adequacy of the evidence on which you rely to support your conclusion that Protykin®, the source of *trans*-Resveratrol, and the new dietary ingredient itself will be reasonably expected to be safe for the following reasons:

- Your notification does not completely disclose the content of Protykin®, provide safety information on it, or demonstrate that its content of *trans*-Resveratrol has the same bioavailability as that found in wine or foods.

Your notification states the source of the new dietary ingredient is a root extract of *Polygonum cupdatum* (Siebold & Zucc.) with the trade name Protykin® that provides a standardized level (50%) of *trans*-Resveratrol. Neither your product specifications sheet nor your certificate of analysis identifies the ingredients that comprise the other 50% of Protykin®. Some or all of these other ingredients may be naturally occurring components of the root extract of *Polygonum cupdatum* (Siebold & Zucc.) that could be biologically active, interactive, or additional new dietary ingredients.

Moreover, none of the information provided in your notification addresses either the safety of Protykin® as the source of *trans*-Resveratrol or the safety of other root extracts of *Polygonum cupdatum* (Siebold & Zucc.) containing *trans*-Resveratrol. Most of the information in your notification pertains to either synthetically produced *trans*-Resveratrol or that naturally occurring in wines and certain foods. It cannot be inferred from the information in your notification that the safety of Protykin®, as a source of *trans*-Resveratrol, is the same as that for foods or that the *trans*-Resveratrol in Protykin® is equally bioavailable as that synthetically produced or that found in wine and foods. Evidence is needed to support your conclusion that long-term daily use of Protykin® is reasonably expected to be safe for the target consumers stated in your notification (i.e., all healthy adults 18 years of age and older, excluding pregnant and nursing women).

¹ See The Institute of Human Virology, University of Maryland Web site at <http://www.ihv.org/pages-new/clinical-tr.html> about the use of resveratrol in Phase I pharmacokinetics clinical trials. The same information about these clinical trials was also published in the Summer 2001 edition of the *IHV Clinical Trials* newsletter produced by The Institute of Human Virology, University of Maryland.

- Your notification does not address some of the possible health concerns about *trans*-Resveratrol consumption raised in the scientific literature.

An article² included in your notification references a study done by Gehm *et. al.* that found that resveratrol can mimic the action of estrogen and stimulate the proliferation of human breast cancer cells (T47D). Your submission does not address whether this possible activity would pose a potential health concern for women who consume *trans*-Resveratrol on a long-term daily basis.

A second article³ in your notification reported that consumption by healthy subjects of commercial grape juice enriched with resveratrol (2 mg/day) for 4 weeks showed reduced thromboxane B₂ synthesis and reduced thrombin-induced platelet aggregation. Your submission does not address the potential safety risk of *trans*-Resveratrol use by persons who also take other platelet aggregation inhibitors (e.g., aspirin) or anticoagulants (e.g., Coumadin).

Another recent article⁴ published in the scientific literature demonstrated that resveratrol is an inhibitor of cytochrome p450 CYP3A4 activity, a prominent mechanism for the metabolism of many drug products. Your submission does not address the potential health concern of *trans*-Resveratrol use by persons who also take drug products or other dietary supplements metabolized by this same enzymatic pathway.

An additional journal article⁵ reported suppression of angiogenesis by resveratrol. This was demonstrated in several models at different exposures, including a relatively low-level oral exposure in mice that inhibited angiogenesis in a corneal neovascularization model. Your submission does not address whether this would be a potential health concern for individuals who consume *trans*-Resveratrol during times when angiogenesis is required, e.g., after injury or during the earliest phases of gestation, before a woman may know that she is pregnant.

In summary, *trans*-Resveratrol is excluded from the definition of a "dietary supplement" under 21 U.S.C. 321(ff)(3)(B). In addition, for the reasons discussed above, the information in your notification does not provide an adequate basis to conclude that either *trans*-Resveratrol or its source, Protykin®, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide

² Kroop, Peter: "Resveratrol, a phytoestrogen found in red wine. A possible explanation for the conundrum of the 'French paradox'," *European Journal of Endocrinology*, 138:619-620, 1998.

³ Pace-Asciak C.R., Rounova, O., Hahn, S.E., Diamandis, E.P., and Goldberg, D.M.: "Wines and grape juices as modulators of platelet aggregation in healthy human subjects," *Clin Chim Acta*, 246:163-182, 1996.

⁴ Chan, W.K. and Delucchi, A.B.: "Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4," *Life Sciences*, 67:3103-3112, 2000.

⁵ Brakenhielm, E., Cao, R., and Cao, Y.: "Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes. *FASEB Journal*, 15(10):1798-1800, 2001.

Page 4 - Mr. Shil C. Kothari

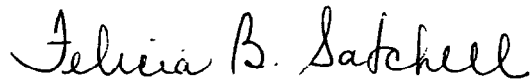
reasonable assurance that it will not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days from the date of its receipt. After December 27, 2001, your notification will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

For FDA's consideration, you may wish to identify in writing specifically what information in your notification you believe is proprietary. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Dockets.

If you have any questions concerning this matter, please contact us at (301) 436-2371.

Sincerely yours,

A handwritten signature in black ink that reads "Felicia B. Satchell". The signature is written in a cursive style with a large, stylized 'F' and 'S'.

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition



OCT 25 2001

Mr. Shil C. Kothari
Product Development Manager
InterHealth Neutraceuticals, Inc.
5451 Industrial Way
Benicia, California 94510

Dear Mr. Kothari:

This is to inform you that the undated notification you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by the Food and Drug Administration (FDA) on September 28, 2001. Your notification concerns the substance "trans-Resveratrol" that you assert is a new dietary ingredient. You describe it in your notification as a root extract of *Polygonum cupdatum* (Siebold & Zucc.) with the trade name Protykin® that provides a standardized level (50%) of trans-Resveratrol.

In accordance with 21 C.F.R. § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after December 12, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains "trans-Resveratrol."

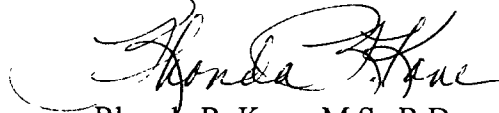
Please note that acceptance of this notification for filing is a procedural matter and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After December 27, 2001, the notification will be placed on public display at FDA's Docket Management Branch (Dockets) in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

Prior to December 27, 2001, you are welcome to identify in writing for us any information in your notification that you believe is proprietary or confidential. Our Freedom of Information Office will consider this when making the final decision about what information should be redacted from the notification before it is sent to Dockets.

Page 2 – Mr. Shil C. Kothari

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Rhonda R. Kane". The signature is fluid and cursive, with a large initial "R" and "K".

Rhonda R. Kane, M.S., R.D.
Consumer Safety Officer
Dietary Supplements Team
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition



(Rec'd)
SEP 28 2001

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204
Telephone Number: (202) 205-4168

To Whom It May Concern:

Please consider the following information as notification of a dietary ingredient:

1. Manufacturer's Name and Address:

InterHealth Nutraceuticals, Inc.
5451 Industrial Way
Benicia CA 94510

2. Name of Dietary Ingredient:

trans-Resveratrol

3. Description of the Dietary Supplement:

- a. *Polygonum cuspidatum* root extract (trade name Protykin[®]) providing standardized levels (50%) of *trans*-resveratrol.
- b. For use as a dietary supplement in capsule, tablet, powder or liquid form.
- c. The recommended dosage as a dietary supplement is 0.5 – 4 milligrams *trans*-resveratrol per day.
- d. Recommended for the general healthy population over the age of 18. Not recommended for pregnant or nursing women. A statement referencing this will be disclosed on the label as a disclaimer.

4. History or Evidence of Safety:

This dietary supplement has been present in the food supply as an article in food and can reasonably be expected to be safe as follows:

- a. *Polygonum cuspidatum* is a traditional Chinese herb known as Hu-chang (pronounced "who-jun") and more commonly as knotweed. The essence and flavor of the root is sour, bitter and mildly pungent with "cold" Chinese medicinal properties. According to the *Oriental Materia Medica*, traditional uses of the root are to clear up "heat," invigorate blood, and detoxify.¹ The Complete German

¹ Hsu H, Chen C, Shen S, Hsu C, Chen C, Chang S, *Oriental Materia Medica: A Concise Guide*, Keats Publishing, New Canaan, Connecticut, 147-148, 1986.

Commission E Monographs lists knotweed as safe with no known side effects or contraindications.² The American Herbal Products Association (AHPA) has also listed *Polygonum cuspidatum* (knotweed) in their 2nd edition of Herbs of Commerce.³

- b. *trans*-Resveratrol, the principle constituent of *Polygonum cuspidatum* root extract, can be found naturally in the human food supply in grape skins⁴, red and white wine^{5,6} and peanuts^{7,8}.
 - i. *trans*-Resveratrol can be found as a constituent of red wine, white wine and grape juice. Scientists believe the attributes of the “French Paradox” have much to do with the consumption of red wine in which *trans*-resveratrol is a constituent.^{9,10} The concentration of naturally occurring *trans*-resveratrol in red wine ranges from less than 1 to 13.4 milligrams per liter (3.4 mg/250 ml glass).⁵ Consumption of 500 milliliters of grape juice per day enriched with 2 milligrams of *trans*-resveratrol significantly reduced blood platelet aggregation compared to non-enriched grape juice.¹¹ The researchers concluded that *trans*-resveratrol can be absorbed from grape juice in biologically active quantities and in amounts that are likely to promote a healthy cardiovascular system
 - ii. Virginia, runner, and Spanish (peanuts), produced in four different locations contained from 0.03 to 0.14 microg of resveratrol/g. Seed coats from runner and Virginia types contained approximately 0.65 microg/g of *trans*-resveratrol, which is equivalent to <0.04 microg/seed. Quantitative analysis of 15 cultivars representing 3 peanut market types, which had been cold stored for up to 3 years, indicated a range of 0.02-1.79 microg/g of peanut.^{7,8}

² Blumenthal M, Busse W, Goldberg A, Gruenwald J, Hall T, Riggins W, Rister R, The Complete German Commission E Monographs, American Botanical Council, 157-158, 1998.

³ McGuffin M, Kartesz J, Leung A, Tucker A, Herbs of Commerce, American Herbal Products Association 2nd Edition, 117, 2000.

⁴ Soleas GJ, Diamandis EP, Goldberg DM: Resveratrol: a molecule whose time has come? and gone? *Clin Biochem* 30:91-113, 1997.

⁵ Goldberg D, Yan J, Ng E, Diamandis EP, Karumanchiri A, Soleas G, Waterhouse AL, A global survey of *trans*-resveratrol concentrations in commercial wines, *Am J Enol Vitic* 46:159-165, 1996.

⁶ Goldberg D, Ng E, Karumanchiri A, Diamandis EP, Soleas GJ, Resveratrol glucosides are important components of commercial wines, *Am J Enol Vitic*. 47:415-420, 1996.

⁷ Sanders TH, McMichael RW Jr, Hendrix KW. Occurrence of resveratrol in edible peanuts, *J Agric Food Chem* 48:1243-6, 2000.

⁸ Sobolev VS, Cole RJ: *trans*-Resveratrol content in commercial peanuts and peanut products, *J Agric Food Chem* 47:1435-9, 1999.

⁹ Kopp P: Resveratrol, a phytoestrogen found in red wine, a possible explanation for the conundrum of the ‘French paradox’? *Eur J Encrinol* 138:619-620, 1998.

¹⁰ Stanley LL, Mazier MJP: Potential explanation for the French paradox. *Nutr Res* 19:3-15, 1999.

¹¹ Pace-Asciak CR, Rounova O, Hahn SE, Diamandis EP, Goldberg D, Wines and grape juices as modulators of platelet aggregation in healthy human subjects, *Clin Chim Acta* 246:163-182, 1996.

- c. *trans*-Resveratrol has also been the subject of much scientific review. A summary of human studies is presented below. None of the studies reported any toxic events.
- i. Oral administration of a single dose of resveratrol (1.5 mg/kg body weight) to ten healthy human volunteers stimulated the release of plasma adenosine (an endogenous nucleoside) level. Adenosine level increased progressively and reached a peak 30min after ingestion and successfully decreased to the starting values at 120 min. Adenosine is considered one of the mediators, if not the only mediator, of the most important spontaneous organic protection against chronic ischemia, a phenomenon known as "ischemic preconditioning". This study demonstrates the promotion of a healthy cardiovascular system from the consumption of *trans*-resveratrol.¹²
 - ii. Resveratrol inhibited peroxidation of the LDL cholesterol obtained from two healthy volunteers by 81% and 70% upon the addition of 10 mmol/lit of resveratrol, thereby promoting a healthy heart. In contrast, 10 mmol/lit of α -tocopherol (natural vitamin E), which has been associated with a reduced risk of heart disease, had a much lower antioxidant potency than resveratrol, inhibiting LDL cholesterol oxidation by only 40% and 19%.¹³
 - iii. Resveratrol lowered platelet aggregation of healthy human blood plasma by 50.3% at a concentration of approximately, 3.5 mg/l. Red wine containing 1.2 mg/l of natural *trans*-resveratrol and 3.6 g/l of polyphenols diluted 1000-fold (final resveratrol concentration: 1.2 mg/l) inhibited platelet aggregation by 42%. By adding resveratrol to wine up to a concentration of 1.2 mg/l, inhibition was raised to 78.5%. These results suggest that the antiaggregating activity of resveratrol is related to its concentration in wine, promoting a healthy cardiovascular system.¹⁴ Resveratrol also inhibited ADP- and thrombin-induced platelet aggregation of healthy human blood plasma in a dose-dependent manner (IC₅₀ of 129.9 and 164.7 mmol/l, respectively).¹⁵
5. **Conclusion:** The preceding information demonstrates that 0.5 – 4 mg *trans*-resveratrol (or 1– 8 mg of Protykin®), the recommended daily dose, is a quantity available from various common dietary sources; has a history of consumption from dietary sources; is an amount consistent with that used in scientific research; and is a dose that can reasonably be expected to be safe.

¹² Blardi P, De Lalla A, Volpi L, Di Perri T: Stimulation of endogenous adenosine release by oral administration of quercetin and resveratrol in man. *Drugs Exptl Clin Res* XXV:105-110, 1999.

¹³ Frankel E, Waterhouse AL, Kinsella JE: Inhibition of human LDL oxidation by resveratrol. *Lancet* 341:1103-1104, 1993.

¹⁴ Bertelli AE, Giovannini L, Giannessi D, Migliori M, Bernini W, Fregoni M, Bertelli A: Antiplatelet activity of synthetic and natural resveratrol in red wine. *Int J Tiss Reac* XVII:1-3, 1995.

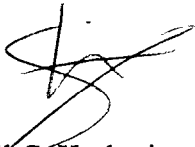
¹⁵ Pace-Asciak CR, Hahn SE, Diamandis EP, Soleas G, Goldberg D, The red wine phenolics *trans*-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease, *Clin Chim Acta* 235:207-219, 1995.

Currently, no claims are being considered for this submission. References used above are to demonstrate safety for human consumption and are not intended as marketing claims. All claims and label copy will be submitted to Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-810).

If more information is required or you should have any questions or comments, please do not hesitate to contact the undersigned.

6. Signature of Manufacturer

Respectfully yours,
InterHealth Nutraceuticals, Inc.

A handwritten signature in black ink, appearing to read 'Shil C. Kothari', with a stylized, flowing script.

Shil C. Kothari
Product Development Manager

Attachments (17)

- 1 – Product Specification Sheet
- 1 – Certificate of Analysis
- 12 – Literature References



RSV-5000 (Powder)

PRODUCT SPECIFICATIONS

DESCRIPTION

Protykin® RSV-5000 is a high-potency, standardized extract of *Polygonum cuspidatum* (root) containing 50% natural *trans*-resveratrol in powder form for use as a dietary supplement.

SPECIFICATIONS

Chemical Classification	Organic, Nutritive
Physical Classification	Powder, Non Fibrous
Color	Medium Brown
Odor	Characteristic Smokey-Herbal
Taste	Characteristic Bitter-Herbal
Plant Part Used	Root
Moisture	Less than 5%
Solubility (alcohol)	75%
Solubility (water)	None
Clarity (1g/100ml water)	Clear Light Reddish – Brown
pH (1g/100ml water)	5.0 – 7.0
<i>trans</i> -Resveratrol (%) by HPLC	50 ± 5
Emodin (%) by HPLC	Less than 2
Heavy Metals:	
Pb (ppm)	Less than 10
As (ppm)	Less than 10
Hg (ppm)	Less than 0.25
Cd (ppm)	Less than 0.25
Particle Size:	
Wt. % Through 100 Mesh	NLT 75
Microbiological Assays:	
Total Plate Count (CFU/g)	Less than 3000
Yeast and Mold (CFU/g)	Less than 10
<i>E. Coli</i> (CFU/g)	Negative
<i>Salmonella</i> (CFU/g)	Negative
<i>Staph. aureus</i> (CFU/g)	Negative
Shelf Life	2 years when stored in tightly closed containers free of excessive heat, moisture, light and air.

PACKAGING

Protykin RSV-5000 is available in 0.1 (minimum), 0.25, 0.5, 1, 2, 4 and 10 kilogram quantities packaged in moisture, air and light-resistant containers.

Product Code RSV-5000

Research Code IH727

Order Code FG14010

PK1-991115-010103

5451 Industrial Way • Benicia, CA 94510 • (707) 751-2800 • FAX (707) 751-2801





Certificate of Analysis

Product:	Protykin
	RSV-5000
Description:	Extract of <i>Polygonum cuspidatum</i>
Part of Plant:	Root
Control Number:	102004
Date of Production:	March 2001
Shelf Life:	2 Years
Analysis Performed By:	Vendor Lab 1
	Vendor Lab 2

Results of Analysis:

Identification:	Passes
Moisture (%):	1.8
Resveratrol (mg/g):	
trans-Resveratrol (mg/g):	541.8
Heavy Metals as Pb (ppm):	<3
Particle Size:	
Wt% Thru 150 Mesh:	86.9
Microbiological Assays:	
Total Plate Count (CFU/g):	<100
<i>E coli</i> :	Negative
<i>Salmonella</i> :	Negative
Yeast:	<10
Mold:	<10
<i>Staph. aureus</i> :	Negative

Confirmation that specification data from independent laboratory is accurately disclosed on this Certificate of Analysis.

InterHealth Nutraceuticals, Inc.

By:

Date

4/27/2001

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